10 years follow up after prenatal transplantation of fetal MSC in a patient with severe osteogenesis imperfecta

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Introduction
Treatment with multipotent mesenchymal stromal cells (MSC) has the potential to ameliorate mesodermal disorders, including bone.

Osteogenesis imperfecta (OI) is a genetic bone disorder leading to repeated fractures and reduced height.

Adult HLA-matched MSC have been used in cellular therapies of OI with promising results (Horwitz, PNAS 2002), MSC are regarded as immunoprivileged cells that could support allogeneic prenatal transplantation.

Prenatal transplantsations have been successfullly performed in children with immunodeficiencies, but has so failed in immunocompetent recipients.

The patient & Transplantation
The patient was diagnosed with OI type III prenatally due to multiple fractures and typical signs of severe OI. Mutation: de novo COL1A2: c.3008G>A, p.Gly1003Asp, Gly913Asp in the triple helix (Le Blanc, Transplantation 2005).

She was transplanted prenatally with 6,5x10⁶ fully HLA mis-matched male fetal MSC in week 32 of gestation and born after cesarean section in week 36.

At 8 years of age she was re-transplanted with 2,8x10⁶ kg same-donor MSC 5 days after a correctional surgery bilateral femoral osteotomy and replacement of rods.

She has developed a scoliosis treated with a brace No fractures for 2 years after re-transplantation.

Engraftment of donor cells
At 9 months
Y-chromosome positive cells were detected in bone.

- 9 months whole chromosome painting: 228 Y-chromosome positive cells/2,500 cells.
- 9 months (6 mon post re-transplantation): 4 Y-chromosome positive cells/60,000 cells.

FISH analysis was performed on bone at 9 months, 6 and 9 years. Y-chromosome positive cells were detected at 9 months and 9 years as indicated by arrows. Donor cells were only detected in bone.

Immunological reaction

The patient has no lymphocyte reaction against donor MSC (figures to the right) or antibodies against donor HLA I or II, IgG or IgM or fetal calf serum (not shown).

Conclusions
Our findings suggest that transplantation of allogeneic fetal MSC in OI is safe and re-transplantation postnatally with same-donor cells is possible.

Fetal MSC can be transplanted across HLA barriers and undergo site-specific differentiation to bone.

Although caution is needed, it seems that the longitudinal growth and fracture incidence has increased after the re-transplantation.

It is not possible from this single case to conclude on beneficial effects of MSC in OI, but an infant with identical mutation (personal communication) who did not receive MSC treatment succumbed at 5 months of age despite postnatal bisphosphonate therapy.

Growth
After re-transplantation and surgery, her linear growth has improved from -6.5 to -6 SD and she is following her own growth curve.

Fracture incidence
At 10 years of age, 12 postnatal fractures and 11 vertebral compression fractures have been confirmed.

4 fractures and 1 vertebral compression fracture have been clinically suspected.

No fractures for 2 years after re-transplantation.

She has developed a scoliosis treated with a brace since 6 years of age.

Clinical course
At present, the the patient is 10 years old and is doing better than expected. Her ability to walk has improved (can walk 1000 meters) and she takes dance classes and participates in modified indoor hockey.

For methodological details see Le Blanc, Transplantation 2005.